Correspondence

Reduction of Nephrotoxicity Associated with Amphotericin B Deoxycholate

SIR—The most compelling argument for replacing amphotericin B deoxycholate (AmBD) with lipid formulations of amphotericin B (LFABs), as proposed by Ostrosky-Zeisner et al. [1], is that it would lead to avoidance of AmBD-associated toxicities, among which nephrotoxicity is the most costly and is associated with the greatest morbidity. However, aggressive hydration and electrolyte correction (as noted by Ostrosky-Zeisner et al. [1] and others [2]), as well as administration via continuous infusion (which is not mentioned by Ostrosky-Zeisner et al. [1], but which has been discussed elsewhere [3, 4]), may significantly reduce the nephrotoxicity associated AmBD. These measures were not systematically used in the comparative trials that showed a reduction in nephrotoxicity with use of LFABs instead of AmBD [1]. Before the much more costly LFABs are adopted for routine use instead of AmBD, it would seem prudent to directly compare the nephrotoxicity of LFABs with that of AmBD administered in a maximally nephroprotective fashion. With respect to the various LFABs, Ostrosky-Zeisner et al. [1] advocate "more head-to-head clinical trials with standardized protocols of infusion and toxicity management…to clearly define which formulation is superior, if any" (p. 423). Perhaps AmBD should be included in such studies.

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Continuous Infusion of Amphotericin B Deoxycholate: A Cost-Effective Gold Standard for Therapy of Invasive Fungal Infections?

SIR—Ostrosky-Zeichner et al. [1] review the toxicity of amphotericin B deoxycholate (AmBD) and recommend the newer, very expensive lipid formulations of amphotericin B (LFABs) as the new gold standard for therapy of invasive fungal infections. Their main concern is nephrotoxicity: up to 30% of patients develop acute renal failure while receiving therapy with AmBD, according to Bates et al. [2]. However, these investigators administered AmBD during a 4-h period and did not hydrate the patients appropriately.

Unfortunately, in their review, Ostrosky-Zeichner et al. [1] did not discuss the published studies carried out by A. Schaffner's research group at our institution [3–5]. Using 24-h continuous infusion of AmBD in treating ~60 severely immunocompromised patients per year, we observe acute renal failure very rarely. This is because we combine antifungal treatment with daily monitoring and aggressive correction of electrolyte levels and hydration. This observation has recently been confirmed clinically and experimentally by another research group [6]. Even in patients receiving high doses (i.e., >1 mg/kg of AmBD in a 24-h continuous infusion) or receiving concomitant treatment with nephrotoxic ciclosporin A, treatment with AmBD very rarely leads to acute renal failure [4, 5].

Equivalent doses of LFABs are ~10 times more expensive than doses of AmBD. We currently save several hundreds of thousands of US dollars per year by not using LFABs. We think it is premature to establish LFABs as the gold standard for therapy of invasive fungal infections. We ask for a study of cost-effectiveness comparing equivalent doses of the new LFABs to 24-h continuous infusion of AmBD. Hospital managers and those interested in cutting health care costs should demand these studies before implementing costly new gold-standard therapies.

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Amphotericin B: Is a Lipid-Formulation Gold Standard Feasible?

SIR—We read with interest the article by Ostrosky-Zeichner et al. [1] proposing that lipid-based formulations of amphotericin B (LFABs) replace amphotericin B deoxycholate (AmBD) as the gold standard for treatment of most invasive mycoses. On the basis of a review of comparative efficacy, toxicity, and cost, we believe AmBD remains a viable first-line agent.

Although the benefits of LFABs have been described in relation to secondary, microbiological end points in clinical trials [2, 3], primary end points have not demonstrated the superior efficacy of LFABs versus AmBD. In a randomized study of patients with histoplasmosis and AIDS, only 1 of 3 primary end points showed an apparent benefit of treatment with liposomal amphotericin rather than with AmBD [4]. The only outcome measurement that demonstrated the superiority of treatment with liposomal amphotericin was "clinical success," which was a composite end point that included the requirement that the patient be afebrile for 3 days. If any fever occurred during that time, including during drug infusion, the treatment was considered a clinical failure. The apparent difference in the efficacy LFABs and AmBD may therefore have been caused by a difference in infusion-related adverse events, rather than by a true difference in efficacy.

Moreover, AmBD-induced toxicities are usually treatable (e.g., infusion reactions) or reversible (e.g., anemia and azotemia) if treatment with the drug is discontinued in a timely manner [5–7]. Patients who develop toxicities can be given an LFAB, limiting the global impact of toxicity caused by the deoxycholate formulation.

Finally, the cost of LFABs is prohibitive. In the year 2000, sales of LFABs in the United States were $180 million, versus $3.3 million for AmBD (table 1). Indeed, despite strictly enforced limitations on their use at our institution, LFABs have been the number one pharmacy cost for each of the previous 5 years. Of the ~1650 drugs administered to patients at Harbor-UCLA Medical Center in 2001, LFABs accounted for 5% of all pharmacy costs.

If LFABs became the new gold standard, the financial impact would be enormous. For example, if 75% of the doses of AmBD administered in the United States in the year 2000 had been administered as LFABs, the additional cost incurred would have been approximately $240 million (75% of 550,000 doses × $580 in additional cost per dose). Although some of the cost differential might be mitigated by savings that result from a decrease in in-

Table 1. Data on sales of amphotericin B (AmB) formulations in the United States, 2000.

Type of AmB, brand name	Quantity per vial, mg	Cost per vial,[a] US$	Daily dose,[b] mg	Estimated no. of vials per daily dose	No. of vials distributed[c]	No. of doses administered[d]	Estimated sales,[c] US$	Estimated cost per dose,[e] US$
LFABs								
Ambisome (liposomal)	50	157	350	7	808,000	115,000	…	…
Abelcet (lipid-complex)	100	85	350	4	739,000	185,000	…	…
	50	NA	350	7	22,200	3,000	…	…
Amphotec (colloidal dispersion)	100	NA	350	4	14,500	3,500	…	…
	50	NA	350	7	2,800	500	…	…
Total	…	…	…	…	1,586,500	307,000	180,000,000	585
AmBD								
Fungizone	50	4.50	35	0.7	345,500	500,000	…	…
Amphotericin B	50	4.50	35	0.7	200,600	290,000	…	…
Amphocin	50	4.50	35	0.7	6,500	10,000	…	…
Total	…	…	…	…	552,600	800,000	3,300,000	4.50

NOTE. AmBD, amphotericin B deoxycholate; LFABs, lipid formulations of amphotericin B; NA, not available.

[a] Data on cost per vial provided by Jennifer Yi of Harbor-University of California Los Angeles Medical Center.
[b] Data assumes a mean body mass of 70 kg and a daily dose of 0.5 mg/kg per day, for AmBD, and 5 mg/kg per day, for LFABs.
[c] Data on no. of vials distributed and estimated sales provided by IMS Health (Fairfield, Connecticut).
[d] No. of doses administered is calculated by dividing the number of vials distributed by the estimated number of vials used per daily dose.
[e] The estimated cost per dose is calculated by dividing the estimated sales by the number of doses administered.